Review

Functional anatomy of movement disorders

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ABSTRACT

Models of basal ganglia function are described which encapsulate the principal pathophysiological mechanisms underlying parkinsonian akinesia on the one hand and abnormal involuntary movement disorders (dyskinesias) on the other. In Parkinson's disease, degeneration of the nigrostriatal dopamine system leads to overactivity of the 'indirect' striatopallidal projection to the lateral (external) segment of the globus pallidus. This causes inhibition of lateral pallidal neurons, which in turn project to the subthalamic nucleus. Disinhibition of the subthalamic nucleus leads to abnormal subthalamic overactivity and, as a consequence, overactivity of medial (internal) pallidal output neurons. Dyskinesias, such as are observed in Huntington's disease, levodopa-induced dyskinesia and ballism, share mechanistic features in common and are associated with decreased neuronal activity in both the subthalamic nucleus and the medial globus pallidus.

Key words: Basal ganglia; Parkinson's disease; akinesia; dyskinesias.

FUNCTIONAL ANATOMY OF THE BASAL GANGLIA

There are 2 simple and robust conceptual models of movement disorders in basal ganglia disease, one describing the neural mechanisms underlying parkinsonian akinesia and the other explaining the appearance of abnormal involuntary movements (dyskinesias). These represent 2 diametrically opposed mechanisms, at opposite ends of the pathophysiological spectrum. Whilst these models are crude approximations to the complexities of human functional anatomy, nevertheless their validity is borne out by their predictive capacity and practical application in new neurosurgical approaches to the treatment of movement disorders, based on manipulation of the globus pallidus and subthalamic nucleus.

The core structures of the basal ganglia are the striatum and globus pallidus (GP), which have close functional associations with the subthalamic nucleus (STN), substantia nigra (SN) and ventral thalamic nuclei. The striatum consists of the caudate nucleus and putamen, which share many similarities of organisation and connections. The putamen is the more overtly motor part of the striatum, receiving connections from the motor areas of the frontal cortex, whilst the caudate nucleus is predominantly connected with more associative cortical regions. The striatum receives the majority of afferent connections to the basal ganglia from extrinsic sources, most notably the dopaminergic nigrostriatal pathway from the pars compacta of the substantia nigra (SNc), a glutamatergic corticostriatal projection and a projection from the intralaminar nuclei of the thalamus. Striatal output neurons, so-called medium spiny neurons, project to 2 main target areas – the globus pallidus and substantia nigra, pars reticulata (SNr). These neurons utilise the inhibitory transmitter, gamma-aminobutyric acid (GABA). The globus pallidus consists of 2 distinct portions, namely the lateral, or external, segment (GPl, GPe) and the medial, or internal, segment (GPm, GPi), both of which receive striatal efferent fibres. Dopamine released from the

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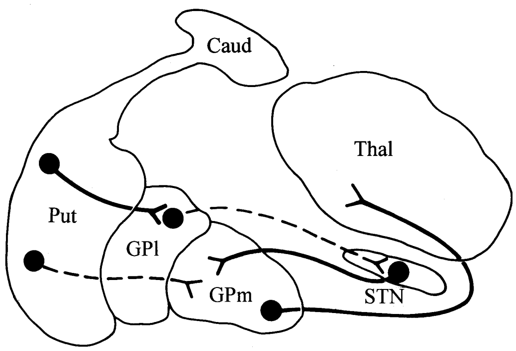

Fig. 1. Semischematic diagram of the basal ganglia and related structures of the diencephalon on the left side, including the principal neuronal interconnections. The changes in neuronal activity which underlie the pathophysiology of parkinsonism are indicated thus: bold lines – abnormally overactive, interrupted lines – abnormally underactive. Caud, caudate nucleus; Put, putamen; GPl, globus pallidus (lateral segment); GPm, globus pallidus (medial segment); STN, subthalamic nucleus; Thal, thalamus.

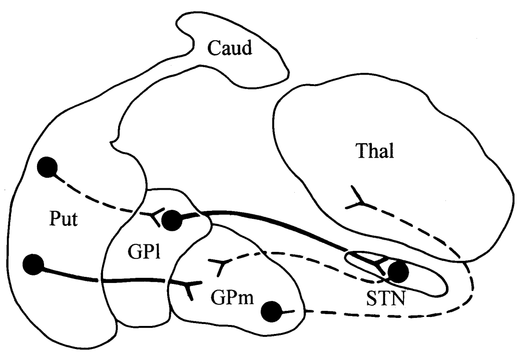

Fig. 2. Semischematic diagram of the basal ganglia and related structures of the diencephalon on the left side, including the principal neuronal interconnections. The changes in neuronal activity which underlie the pathophysiology of dyskinesia are indicated thus: bold lines – abnormally overactive, interrupted lines – abnormally underactive. Caud, caudate nucleus; Put, putamen; GPl, globus pallidus (lateral segment); GPm, globus pallidus (medial segment); STN, subthalamic nucleus; Thal, thalamus.

nigrostriatal pathway appears to have opposite functional effects on the 2 striatopallidal cell populations (Penney & Young 1983, 1986). Thus it inhibits striatal neurons which project to the lateral segment of the globus pallidus and excites neurons which project to the medial segment.

The 2 segments of the globus pallidus have distinct afferent and efferent connections. The medial segment is regarded (together with the pars reticulata of the substantia nigra) as the principal output of the basal ganglia, since the majority of fibres projecting to other parts of the neuraxis originate there. The main source of afferents to the GPm is the striatum. This is the so-called 'direct pathway', since it directly controls the activity of medial pallidal output cells. The neurons of the direct pathway synthesise the peptides substance P and dynorphin. The largest efferent projection of GPm is to the thalamus, fibres ending predominantly in ventral tier nuclei (ventral anterior and ventral lateral nuclei, VA and VL) and the intralaminar nuclei. The VA and VL nuclei in turn project to motor regions of the cerebral cortex, especially to the premotor and supplementary motor areas of the frontal lobe. In addition, the medial pallidal segment sends a small projection to the pedunculopontine nucleus (nucleus tegmenti pedunculopontinus; PPN) of the caudal midbrain. Medial pallidal efferents are GABAergic. The GPl also receives a major GABAergic projection from the striatum. This is the origin of the so-called 'indirect pathway', since it influences the activity of GPm cells indirectly, through a connection with the subthalamic nucleus. The GPl sends a major projection to the subthalamic nucleus and also establishes intrapallidal connections from lateral to medial segments. Both of these pathways are GABAergic. The subthalamic nucleus also receives input from the cerebral cortex and intralaminar thalamic nuclei. The major outputs of the STN are excitatory glutamatergic projections are to the globus pallidus and SNr. The basal ganglia connections outlined above are one of several parallel circuits which interconnect striatal, thalamic and cortical levels (Alexander et al. 1990).

In functional terms, activity in the indirect pathway, transmitted through the GPl- STN- GPm-thalamic – cortical circuit, is thought to be responsible for inhibiting unwanted or inappropriate movement/behaviour. Activity in the direct pathway, on the other hand, is thought to facilitate and reinforce intended, behaviourally relevant motor behaviour.

PARKINSONISM

Parkinson's disease is the commonest basal ganglia disorder and is characterised by akinesia/bradykinesia, rigidity and tremor. The central neuropathology is degeneration of the dopaminergic neurons of SNc, which form the nigrostriatal tract. Elucidation of the pathophysiological mechanisms underlying parkinsonism was greatly facilitated by the discovery that the neurotoxin N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) produced parkinsonism in man (Davis et al. 1979; Langston et al. 1983) and monkeys (Burns et al. 1983, 1984; Chiueh et al. 1984) accompanied by nigral pathology (Burns et al. 1984; Chiueh et al. 1984; Langston et al. 1984). The MPTP primate model of Parkinson's disease has provided much insight into the neural mechanisms mediating parkinsonian symptoms and has led directly to advances in human treatment. In particular, 2-deoxyglucose (2-DG) uptake studies and single unit recording in primates have demonstrated the changes in basal ganglia pathways that follow dopamine loss. 2-DG studies revealed an increase in metabolic activity in the GPl in MPTP-induced parkinsonism (Crossman et al. 1985, 1987; Mitchell et al. 1986, 1989). This indicated overactivity of the 'indirect' striatopallidal projection to GPl. This causes inhibition of lateral pallidal neurons, which in turn project to the STN. Disinhibition of the STN leads to abnormal STN overactivity and, as a consequence, overactivity of medial pallidal output neurons.

These studies, demonstrating that parkinsonism is associated with abnormal overactivity of the medial segment of the globus pallidus, were in accord with the findings of single unit recording studies in MPTP monkeys, in which it was reported that GPm neurons exhibit abnormal patterns of spontaneous activity and abnormally enhanced responsiveness (DeLong, 1990; Filion & Tremblay, 1991). The 2-DG studies provided evidence, for the first time, that the subthalamic nucleus is involved in the pathophysiology of parkinsonism (Crossman et al. 1987; Mitchell et al. 1989), a finding which was confirmed in single unit recording studies (Bergman et al. 1994). The significance of these findings for the treatment of human disease was demonstrated in experiments where the blockade of overactive subthalamopallidal transmission, by direct injection of a glutamate antagonist into the GPm, was found to completely alleviate parkinsonism in the MPTP monkey (Graham et al. 1990; Brotchie et al. 1991). These findings provided the essential experimental background for recent developments in the neurosurgical treatment of Parkinson's disease in man by posteroventral pallidotomy (Laitinen 1994; Dogali et al. 1995; Baron et al. 1996). The use of subthalamic nucleus manipulation to treat human Parkinson's disease has also received considerable recent interest. This is because it has been shown in the MPTP primate model that lesions of the overactive STN alleviate parkinsonism (Bergman et al. 1990; Aziz et al. 1991, 1992). A small number of subthalamotomies have been reported in man with encouraging results and dramatic improvement in parkinsonian patients has been reported following subthalamic nucleus stimulation through indwelling electrodes (Benazzouz et al. 1993; Benabid et al. 1994; Limousin et al. 1995). This procedure probably causes depolarisation blockade of STN neurons, thus mimicking the effect of a subthalamic lesion.

BALLISM, CHOREA AND L-DOPA-INDUCED DYSKINESIA

Ballism is a vigorous, forceful, hyperkinetic movement disorder, sometimes producing flailing movements because of the involvement of the proximal limb and associated axial musculature (Barbeau et al. 1981). It is the only abnormal involuntary movement disorder produced by a single, small lesion in a specific brain nucleus. Whittier (1947) concluded that ballism is almost invariably associated with lesion of the subthalamic nucleus.

The first animal model of a human basal ganglia disorder to be subjected to systematic functional analysis was ballism in the macaque monkey, produced by lesion of the STN (Whittier & Mettler, 1949; Carpenter et al. 1950). At least 20% of the nucleus had to be destroyed to induce dyskinesia. This model, and subsequently developed variations based on pharmacological manipulation of the STN, have been highly informative of the mechanisms of dyskinesia. Ballism was completely abolished by lesions of the globus pallidus (Whittier & Mettler, 1949; Carpenter et al. 1950). Since the lateral segment projects principally to the subthalamic nucleus, which was the site of the provocative lesion, the ameliorating effect of pallidal lesions was concluded to be due to involvement of the GPm. This agrees with the human surgical literature which describes the beneficial effects on various dyskinesias, including ballism, of lesions placed in the globus pallidus or its efferent projection system to the thalamus (Cooper, 1969). The GPm projects principally to the VL and VA thalamic nuclei. Ballism in monkeys was ameliorated by lesions of the ventral thalamic area (Carpenter et al. 1950) which, once again, is in accordance with an extensive human surgical literature on thalamic surgery for movement disorders (Martin & McCaul, 1959; Cooper, 1969). Ventral thalamic nuclei are the main route by which the basal ganglia influence motor areas of the cerebral cortex, principally to the premotor and supplementary motor cortices (Asanuma et al. 1983; Schell & Strick, 1984). Ablation of the premotor cortex in the monkey was without effect on dyskinesia, but when lesions were extended to include the primary motor cortex, it was abolished in association with the appearance of contralateral hemiparesis (Carpenter & Mettler, 1951). Similar observations were made in man during the early days of neurosurgical procedures for dyskinesias, including ballism (Bucy, 1948; Alpers & Jaeger, 1950). Transection of spinal white matter tracts showed that dyskinesia was only abolished by destruction of the dorsal portion of the lateral funiculus (through which run the corticospinal and rubrospinal tracts) but this too was associated with hemiparesis (Carpenter et al. 1960). Lesions of the ventral part of the lateral funiculus (carrying the medullary reticulospinal tracts and lateral vestibulospinal tracts) or the ventral funiculus (carrying the pontine reticulospinal tracts and medial longitudinal fasciculus) had no such effect. In summary, the evidence indicated that abnormal activity sustaining dyskinesia following a subthalamic lesion is channelled through the medial globus pallidus, ventral thalamus, cerebral cortex and corticospinal tract.

At the time of these studies, it was generally believed that the subthalamic nucleus exerted an inhibitory influence upon the globus pallidus, using GABA as its transmitter. Ballism was, therefore, regarded as a 'release phenomenon', whereby the globus pallidus was relieved of subthalamic inhibition and was, thus, responsible for the generation of abnormal activity. Furthermore, the subthalamic nucleus was regarded as significant only insofar as its relationship to the rare condition of ballism and it was not considered to be of further consequence in motor function or movement disorders. As a result of more recent research, however, the physiological function of the subthalamic nucleus has been completely revised and it has been discovered to have a crucial role in basal ganglia function, being implicated in several forms of dyskinesia and in Parkinson's disease itself.

Ballism can be induced in primates by intracerebral injection of GABA antagonists into the subthalamic nucleus (Crossman et al. 1984). This induces depolarisation blockade of subthalamic neurons, mimicking a subthalamic lesion. 2-DG analysis of ballism showed a reduction in accumulation in both segments of the globus pallidus and in the SNc, the main output targets of the subthalamic nucleus (Mitchell et al. 1989). This indicated reduced activity of subthalamopallidal and subthalamonigral terminals, consistent with reduced STN activity. Quite contrary to expectation, however, decreased 2-DG uptake was also found in the VA and VL thalamic nuclei, indicating a concomitant reduction in neuronal activity in the pallidothalamic pathway. This interpretation was supported by a decrease in 2-DG uptake in the PPN nucleus, the brainstem termination of GPm efferents. This constituted the first physiological evidence, in a behavioural model, that the subthalamic nucleus in fact exerts an excitatory, rather than an inhibitory, influence on the output of the basal ganglia. This was subsequently confirmed in electrophysiological recording studies (Kita & Kitai, 1991; Nakanishi et al. 1991). The evidence suggests that the transmitter in subthalamic efferents is glutamate. Immunocytochemistry shows glutamate immunoreactivity in subthalamic cell bodies (Smith & Parent, 1988) and glutamate receptor antagonists block subthalamopallidal transmission in electrophysiological experiments (Nakanishi et al. 1991). In neurochemical studies a high-affinity transmitter uptake system for glutamate was identified in the pallidum, which was specifically depleted by subthalamic nucleus lesions (Brotchie & Crossman, 1991).

The paradox of decreased STN-mediated excitation of the GP in ballism and the well-established ability of pallidal lesions to abolish dyskinesia, indicated that the simplistic notion of decreased pallidal activity per se as being the central mechanism in dyskinesia, was too naive. It was concluded that it must be the precise temporal pattern of abnormal medial pallidal activity which sustains dyskinesia.

Chorea describes abnormal involuntary movements characterised by 'excessive, spontaneous movements, irregularly timed, non-repetitive, randomly distributed and abrupt in character' (Barbeau et al. 1981). It usually involves the distal parts of the extremities and the orofacial musculature. The classical form of chorea occurs in Huntington's disease, an inherited neurodegenerative disease in which there is atrophy of the striatum and cerebral cortex. There is a profound loss of GABA, the transmitter utilised by striatal efferent fibres, and enzymic markers of GABA metabolism such as glutamate decarboxylase (GAD) from the basal ganglia in the postmortem Huntington's brain (Bird et al. 1973; Bird & Iversen, 1974).

Chorea can be produced experimentally in primates by localised blockade of GABA transmission in the lateral globus pallidus (Crossman et al. 1984; Jackson & Crossman, 1984). This corresponds with the finding that enkephalin, which is colocalised with GABA in the striatal projection to the GPl, is selectively depleted early in the disease, when chorea is often prominent (Albin et al. 1991; Sapp et al. 1995). In contrast, substance P, which is colocalised with GABA in the direct pathway to the GPm, is relatively preserved (Beal et al. 1988). 2-DG metabolic mapping in monkeys (Mitchell et al. 1989) showed that when chorea was elicited by blockade of striatopallidal transmission in the GPl, there was an increase in 2-DG accumulation by the ipsilateral STN. Analysis of the topography of 2-DG uptake in the STN demonstrated that it was due to overactivity of the pallidosubthalamic pathway, induced by loss of striatopallidal inhibition. These experiments simultaneously demonstrated that chorea was associated with decreased neuronal activity in both the STN and GPm. These studies thus provided a possible mechanism for the choreiform movements of Huntington's disease and suggested a functional link between chorea and ballism (Mitchell et al. 1985).

L-DOPA-induced dyskinesia is a common complication of the long-term treatment of Parkinson's disease with L-DOPA. The development of dyskinesia appears to be dependent on activation of striatal dopamine receptors, although receptor supersensitivity alone is insufficient explanation. Dyskinesia has been linked to the pulsatile mode of drug delivery but the cascade of events linking dopamine receptor stimulation to the appearance of dyskinesia is unclear. MPTP-exposed primates display all of the major motor complications of long-term L-DOPA treatment in man including L-DOPA-induced dyskinesia (Clarke et al. 1987; Crossman et al. 1987; Boyce et al. 1990). 2-DG metabolic mapping studies (Mitchell et al. 1990, 1992) indicate low functional activity in the indirect striatal pathway to the GPl (Crossman, 1990). This causes disinhibition of GPl neurons, which in turn leads to physiological inhibition of the subthalamic nucleus and, thus, decreased activity of medial pallidal output neurons to the thalamus. It has been proposed, therefore, that all forms of choreic movement disorders so far subjected to detailed analytical study share the same common underlying mechanism, the central features of which are abnormal underactivity of the subthalamic nucleus and the medial pallidal segment.

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